OMB INFORMATION COLLECTION
0910-0308

Adverse Experience Reporting for Licensed Biological Products; and General Records
21 CFR 600

SUPPORTING STATEMENT

A). JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting an extension of OMB control No. 0910-0308 and OMB approval of the following information collection requirements in 21 CFR 600.12, 600.80, 600.81, and 600.90 (Attachment A):

21 CFR 600.80(c)(1)	Reporting	Requires the licensed manufacturer to report each adverse experience that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information.
21 CFR 600.80 (c) (2)	Reporting	Requires the licensed manufacturer to report all adverse experiences in a narrative summary, not reported under paragraph (c) (1) (i) at quarterly intervals for 3 years from the date of issuance of the product license, and then at annual intervals.
21 CFR 600.80(e)	Reporting	Requires the licensed manufacturers to submit a 15-day Alert report obtained from a postmarketing clinical study only if there is a reasonable possibility that the product caused the adverse experience.
21 CFR 600.81	Reporting	Requires the licensed manufacturers to report semiannually the quantity of the product distributed under the product license, including the quantity distributed to distributors.
21 CFR 600.90	Reporting	Requires a licensed manufacturer to submit a waiver request with supporting documentation for waiving the requirements under 21 CFR 600.80 and 600.81.

21 CFR 600.80 (i)	Recordkeeping	Requires records of all adverse experiences to be maintained for ten years.
21 CFR 600.12 (a), (c), (d), & (e)	Recordkeeping	Requires records of each step in the manufacture and distribution of a product to be maintained for a prescribed period of time.
21 CFR 600.12 (b)(2)	Recordkeeping	Requires records to be maintained pertaining to the recall from distribution of any product.

Under the Federal Food, Drug, and Cosmetic Act (the Act)(21 U.S.C. 201 et. seq.) and the Public Health Service Act (42 U.S.C. 262, 264)(See Attachment B), FDA is required to ensure the marketing of only those biological products that are shown to be safe and effective. FDA must, therefore, be promptly informed of all adverse experiences occasioned by the use of licensed biological products. FDA promulgated information requirements in 21 CFR §§600.80 and 600.81 which would enable FDA to take actions necessary for the protection of the public health in response to reports of adverse experiences related to licensed biological products. The licensed manufacturers are required to report to FDA on all serious and unexpected adverse reactions regardless of the source from which the manufacturer obtained the reaction information. These reports are filed using the MedWatch Form FDA-3500A (approved under OMB No.0910-0291) (See Attachment C); or the Vaccine Adverse Experience Reporting System Form (VAERS-1) (See Attachment D). The National Childhood Vaccine Injury Act (NCVIA)(42 U.S.C. §300aa-1)(Section 321of Pub. L. 99-660) specifically addresses the waiver of paperwork reduction in the implementation of this statute. A manufacturer may also use an alternative report form provided the format is equivalent to all elements of information specified in the designated forms and the format is pre-approved by MedWatch or VAERS.

The general recordkeeping provisions under §600.12 requires manufacturers to maintain records of each step in the manufacture and distribution of products. These requirements provide FDA with the necessary information to help ensure the safety, purity, and potency of biological products.

2. <u>Purpose and Use of the Information</u>

The adverse experience reporting (AER) system flags potentially serious safety problems with licensed biological products, focusing especially on newly licensed products. Although pre-market testing discloses a general safety profile of a new drug's comparatively common adverse effects, the larger and more diverse patient populations exposed to the licensed biological product provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects. Reports are obtained from a variety of sources, including patients, physicians, foreign regulatory agencies, and clinical investigators. Information derived from the adverse experience reporting system contributes directly to increase public health protection because such information enables the FDA to recommend important changes to the product's labeling (such as adding a

new warning) and, when necessary, to initiate removal of a biological product from the market and to assure the manufacturer has taken adequate corrective action, if necessary. The semiannual distribution report allows FDA to see the quantity, the lot number, and the dosage of different products. This allows FDA to estimate more accurately the incidence of a product's adverse effects in relation to the volume of the product distributed.

The recordkeeping requirements serve preventative and remedial purposes by requesting accountability and traceability in each step from the manufacture to distribution and recall of products and by enabling FDA to perform meaningful inspections.

Without this information, FDA could not monitor industry procedures and discharge its statutory responsibility for protecting the nation's health.

3. Use of Information Technology and Burden Reduction

Licensed manufacturers may use computers, tapes, microfiche or microfilm in lieu of hard copy records for the purpose of maintaining records. Computers may be used for filing distribution records.

We are not aware of any other improved technology to reduce the burden.

4. Efforts to Identify Duplication and Use of Similar Information

This information is only required by FDA. No other agency requires similar information or data to be filed. This information is not available from any other source.

5. Impact on Small Businesses or Other Small Entities

FDA believes that the regulations should apply equally to all enterprises. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help to small businesses. CBER's Office of Communication, Training and Manufacturers Assistance provides guidance to small businesses concerning regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

Less frequent data collection would delay identification of biological products believed responsible for adverse reactions including permanent injuries and fatalities. Appropriate FDA action such as withdrawal from the market or changes in labeling would be delayed by less frequency.

There are no technical or legal obstacles to reducing the burden.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

Licensed manufacturers are required to submit to FDA a 15-day Alert report for each adverse experience. This requirement enables FDA to promptly investigate, and when necessary, initiate corrective action to protect the public from potential adverse product interactions.

The AER regulations require retention of records for a period of 10 years. The 10-year retention period is to assure that a respondents records, which include raw data and any correspondence relating to an adverse drug experience, are available in evaluating long-term or other rare or latent effects such as disease transmission or carcinogenicity that might be detected after several years of marketing experience.

Under §600.12, the retention of records are required to be maintained no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual products, whichever represents a later date. The retention period is necessary because of the incubation periods of some transmissible diseases that might occur from biological products. Since it may take several years for a disease that was transmitted to manifest itself and if a manufacturer needs to do a thorough investigation, they would need the manufacturing records. In addition, many biologics are intended to directly affect cellular functions and it may take considerable time to detect subtle changes in cellular functions resulting from problems with a biological product.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

In accordance with 5 CFR 1320.8(d), a 60-day notice for public comment on the information collection provisions was published in the **Federal Register** of July 10, 1998, (63 CFR 37394, Attachment E). Two comments were received in response to the 60-day notice.

Both comments agreed there is practical value in this proposed collection of information. However they questioned the estimate of the annual responses and provided estimates of burden hours for 21 CFR 600.80(c)(2). Based on these comments and further internal research, the burden chart for this collection of information was revised. In addition, the annual number of responses was revised and the basis of estimate clarified as follows. A periodic report may include zero to hundreds of individual MedWatch and VAERS-1 Forms. These forms are attached to the report. The original estimate of periodic reports (5,903) was the total number of these individual forms, whereas the current estimate (1,129) reflects the number of periodic reports received regardless of the number of attachments. More than half of these reports are monthly reports on plasma derivatives that should take about 2 hours each to complete. The balance of the reports are quarterly and annual reports that may require an average of 28 hours to prepare. The burden hours required to complete the MedWatch Form for §600.80(c)(1), (e), and (f) are reported under OMB Control No. 0910-0291. The VAERS-1 Form is exempt because Section 321 of the National Childhood Vaccine Injury Act (NCVIA) specifically addresses the

waiver of paperwork reduction in the implementation of this statute.

Both comments questioned the statement that there were no capital operating or maintenance costs associated with the ten year maintenance period. FDA believes there are no maintenance costs associated with the storage/retention of records because respondents already have the facilities and the infrastructure for on-going record retention, and that existing and emerging data storage technology minimizes space and costs of long-term record retention.

Both comments recommended ways to enhance the quality, utility, and clarity of the information to be collected, and to minimize the burden of the collection of information on the respondents. FDA is in the process of revising its safety reporting and recordkeeping regulations and will consider their comments in developing its rulemaking. FDA has provided notice and requested comments on several proposed rules. In the Federal Register of October 27, 1994 (59 FR 54046), FDA published a proposed rule to amend its postmarketing expedited and periodic safety reporting requirements, as well as others, to implement international standards and to facilitate the reporting of adverse drug experiences. In the Federal Register of October 27, 1997 (62 FR 52237), FDA published a final rule amending its expedited safety reporting regulations to implement certain recommendations in the ICH E2A guidance on definitions and standards for expedited reporting. At this time, the agency is further considering recommendations in the ICH E2A guidance for additional amendments to its postmarketing expedited safety reporting regulations. With respect to the proposed amendments to the periodic adverse drug experience reporting requirements in the proposal of October 27, 1994, FDA has decided to repropose these amendments based on recommendations in the ICH E2C guidance on periodic safety update reports. In developing the reproposal, FDA will also consider comments submitted in response to the proposed rule of October 27, 1994, regarding periodic adverse experience reports. FDA is also considering rulemaking concerning the electronic submission of postmarketing expedited and periodic safety reports using standardized medical terminology, data elements, and electronic transmission standards recommended by the International Conference on Harmonization (ICH). The respondents to the collection of information discussed here will, therefore, have further opportunity to provide comment on these rulemaking initiatives.

The most recent consultations with outside sources has been FDA's participation in the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use and with the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS). These organizations have met periodically over the past five years to facilitate international consideration of issues, particularly safety issues, concerning the use of both foreign and domestic data in the development and use of drugs and biological products. The organizations include representatives from government, associations , and the pharmaceutical industry (including PHRMA) from the European Union, Japan, and the U.S.. ICH has produced several adverse drug reaction reporting guidances that pertain to expedited safety reporting, periodic safety reporting, and electronic submission of reports. FDA is currently revising its regulations to be consistent with the ICH recommendations.

9. Explanation of Any Payment or Gift to Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents.

10. Assurance of Confidentiality Provided to Respondents

The confidentiality of information received by FDA is consistent with the Freedom of Information Act and the Agency's published regulations of "Public Information" under 21 CFR Part 20 which prohibit FDA from releasing to the public the names of patients, individual reporters, health care practitioners, hospitals, and any geographical identifiers.

11. Justification for Sensitive Questions

Questions of a sensitive nature are not applicable to this information collection.

12. Estimates of Hour Burden Including Annualized Hourly Costs

The estimated annual burden for this information collection is 342,132 hours.

Estimated Annual Reporting Burden					
21CFR Section	No. Of Respondents	No. Of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
600.80(c)(1) & 600.80(e)	69	23.4	1,616	1	1,616
600.80 (c)(2)	69	16.4	1,129	28	31,612
600.81	69	6.7	464	1	464
600.90	3	1	3	1	3
				TOTAL BURDEN HOURS	33,695

The total number of respondents in the chart, is based upon information submitted to FDA in fiscal year (FY)1996, which shows that 69 licensed manufacturers (excluding 3 manufacturers who received waivers from AER requirements, produced 242 licensed biological products. The 69 licensed manufacturers excludes those manufacturers who only produce blood and blood components or in-vitro diagnostic licensed products and are exempt from the AER regulations. In FY96, licensed manufacturers submitted approximately 1,616 15-day Alert reports under §§600.80(c)(1) and 600.80(e), 1,129 periodic reports under §600.80(c)(2); and 464 distribution

reports under §600.81. The MedWatch Form that is used to submit the information provided under §600.80(c)(1), (e), and (f) has received approval under OMB Control No. 0910-0291.

Estimated Annual Recordkeeping Burden					
21 CFR Section	No. Of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
600.12 (a), (c), (d) & (e)	102	88.5	9,027	2,832	288,864
600.12 (b) (2)	391	1.8	710	43	16,813
600.80(i)	69	39.8	2,745	40	2,760
				TOTAL	308,437

There are approximately 391 licensed manufacturers of biological products. The number of recordkeepers under §600.12(a), (c), (d), and (e) is estimated to be 102. That number excludes the 189 manufacturers of blood and blood components whose recordkeeping is conducted pursuant to § 606.160, which is approved under OMB Control No. 0910-0116. FDA expects that the total number of AER records kept by the respondent will parallel the total number of reports submitted to FDA. The total number of annual records, therefore, is based on reporting information provided to FDA by manufacturers. Based on FY96 data, the total annual records are estimated as follows: under §600.12(a), (c), (d), and (e), the number of lots released was 9,027; under §600.12(b)(2), the number of recalls was 710; and under §600.80(i), the total number of AER reports received was 2,745. Based on FDA's experience, the agency estimates that the total number of hours per recordkeeper under §600.12(a), (c), (d), and (e) would be 32 hours per lot multiplied by 88.5 lot records on the average per recordkeeper, totaling 2,832 hours; the total number of hours per recordkeeper under §600.12(b)(2) would be 24 hours per recall multiplied by 1.8 recalls on the average per recordkeeper, totaling 43 hours; and the total number of hours per recordkeeper under §600.80(i) would be 1 hour per report multiplied by 39.8 AER records on the average per recordkeeper, totaling 40 hours.

Cost to Respondents

The estimated annualized cost to the respondents is $8,782,529.00. This cost is based on a pay rate of $25.67 per hour for a mid level professional who has the training and skills to handle the various reporting and recordkeeping requirements. This salary estimate includes benefits but no overhead costs.

Cost to Respondents			
Activity	Number of Hours	Cost per Hour	Total Cost
Reporting	33,695	$25.67	$864,951.00
Recordkeeping	308,437	$25.67	$7,917,578.00
		TOTAL	$8,782,529.00

13. Estimate of Other Total Annual Cost Burden to Respondents or Record-keepers

There are no capital, operation, and maintenance costs associated with the collection of information requirements.

14. Annualized Costs to the Federal Government

The estimated annual cost to the government is $36,378.00. This figure is based on a GS-6 Consumer Safety Technician, at a pay rate of $12.97, who is responsible for triage of the report This figure is also based on a GS-13 Consumer Safety Officer, at a pay rate of $30.39 per hour, who is responsible for reviewing the reports.

Annual Cost to Federal Government				
Activity	Number of Report	Hours per Report	Cost per Hour	Total Cost
Report Triage	3,212	0.1	$12.97	$4,166.00
Report Review	3,212	0.33	$30.39	$32,212.00
			TOTAL	$36,378.00

15. Explanation of Program Changes or Adjustments

The estimated total annual burden for the AER information collection requirements was 8,329 hours in 1995. The current increase to 342,132 burden hours is mostly attributable to the revised estimate and addition to this information collection package of the recordkeeping requirements under §600.12 (305,677 hours), and to a lesser degree, the increase in the number of 15-day Alert reports under §600.80(c)(1). There is a slight reduction in burden due to the revocation of the requirement §600.80 (c) (1) (ii) for increased frequency reports as expedited reports for human drug and licensed biological products, (62 FR 34166, June 25, 1997).

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

FDA is not seeking approval to exempt display of the expiration date for OMB approval.

18. Exception to Certification for Paperwork Reduction Act Submissions

There are no exceptions to Item 19 of OMB Form 83-I.